REMARKS/ARGUMENTS

Applicants acknowledge with appreciation the withdrawal of objections and rejections to the claims and specification as detailed in the Office Action.

Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 are pending in the application. New claim 125 has been added. Support for the newly added claim can be found in the original claims as well as in the specification, particularly on pages 7-8. No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Rejection of Claims Under 35 U.S.C.§112, First Paragraph, Should Be Withdrawn

The Office Action (4/28/03, page 8, #26) has rejected claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

The Office Action (page 9) states that:

> [T]he instant specification does not teach that the interaction of monoclonal antibodies is indicative of native conformation. In fact, as clearly known in the art, the interaction of any particular antibody with its antigen (protein) relies solely on the presence of an epitope. An assay with a monoclonal antibody merely tests for the conformation of the epitope, and NOT the conformation of the entire 218 amino acid protein.

Applicants agree that the reactivity of antibodies depends on the presence of an epitope. However, Applicants note that the claims are drawn to utilizing a ***set*** of interacting molecules capable of binding with the native protein. The notion of using a set or panel of interacting molecules is addressed throughout the specification, particularly for example on page 5, and is illustrated in the Experimental section on page 13 ("a panel of 21 monoclonal antibodies recognizing wild-type VSP has been characterized by ELISA."). These points were emphasized and illustrated in the Rule 132 declaration submitted in the case on March 29, 2002 (see particularly, for example, numbers 5 and 6; and the Experiments described in the declaration).

The Experiments described in this Rule 132 declaration illustrate that one of skill in the art can readily make and evaluate a set of monoclonal antibodies that recognize an array of epitopes which are present on the native protein but are absent when the conformation of that protein is altered.

Thus, in contrast to the conclusion reached in the Office Action, the claimed methods of the invention do not purport to determine whether the engineered protein has the conformation of the native protein using only a single antibody or interacting molecule. Rather, the claimed methods involve the use of a ***set*** of antibodies or interacting molecules, and the data gathered from the reactivity of this set allows one of skill to determine whether or not the conformation of the engineered protein is altered in comparison to the conformation of the native protein. One of skill appreciates that the larger the set of antibodies or interacting molecules that is used in such a method, the more reliable is the evaluation of the conformation of the engineered protein. Applicants do not represent that the claimed methods are as conclusive as three-dimensional crystal structure data; instead, the advantage of these methods is that they provide a relatively quick and easy method for determining whether an engineered protein has an altered conformation as evaluated by the chosen set of interacting molecules.

Similarly, claims such as claim 119 that are drawn to the use of proteins that form homodimers or heterodimers with the native protein of interest do not depend for their binding capabilities on a single portion of the protein but instead are expected to have multiple contact points that are important for binding; thus, the binding of such proteins to each other serves as an assay of the conformation of more than one portion of the engineered protein.

The Office Action (page 11) states that "it is wholly unpredictable whether or not the native conformation (or even a conformation recognized by the monoclonal antibody described) can be maintained with such extensive modification to the small protein sequence" and "[n]o direction as to the allowed changes for every known protein in the art is taught." Applicants note that, in order to clarify the claimed invention, the claims have been amended to recite that the second part of the method step involves determining whether said engineered protein has the conformation of the native protein. Although Applicants believe that the claims as previously presented were clear, the claims as amended no longer require that the engineered protein retains

the conformation of the native protein. Thus, the claims as amended require introducing amino acid changes into a native protein of interest and determining whether said engineered protein retains the conformation of the native protein.

Accordingly, for the reasons discussed above, Applicants respectfully submit that the rejection of claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

The Office Action (4/28/03, page 8, point #25) has rejected claim 99 under 35 U.S.C. §112, first paragraph, "as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Claim 99 has been amended to omit the phrase beginning "rather than" to clarify the claim. Support for the amino acid changes of the claimed method being substitutions can be found in the specification, particularly on pages 6-7. Accordingly, this rejection should be withdrawn.

The Rejection of Claims Under 35 U.S.C.§112, Second Paragraph, Should Be Withdrawn

The Office Action (4/28/03, page 6, #20) has rejected claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 as being indefinite for lack of clarity as to whether "the 'said [conformation]' item (either item c or d) is unclear as to whether or not it is a method step." Applicants appreciate the Examiner's suggestions for modifying these claims and have amended independent claims 54, 58, 69, and 97 in accordance with the Examiner's suggestions to clarify the steps of the claimed method. Accordingly, claims which are dependent on these amended independent claims have also been amended. Such claims include claims 55-57 and 119-124 (dependent on or incorporating the limitations of claim 54), claims 60-68 (dependent on or incorporating the limitations of claim 58), claims 70-83 (dependent on or incorporating the limitations of claim 69), and claims 98-107 (dependent on or incorporating the limitations of claim 97). Accordingly, this rejection should be withdrawn.

The Office Action (4/28/03, page 6, #21) has rejected claims 64 and 79 as being indefinite for confusing or incorrect claim dependency. Applicants appreciate the Examiner's suggestions for modifying these claims and have amended the claims in accordance with the Examiner's suggestions: claim 64 has been amended to depend from claim 63; and claim 79 has been amended to depend from claim 78. Accordingly, this rejection should be withdrawn.

The Office Action (4/28/03, page 6, #22) has rejected claims 64, 79, 103, and 123 as being indefinite for being confusing due to their apparent implication that phage display methodology was used for random mutagenesis rather than for assessing the random mutants produced by mutagenic PCR or DNA shuffling. Applicants note that in this rejection the Office Action apparently intended to reject claim 104, which mentions mutagenic PCR, DNA shuffling, and phage display methodology, rather than to reject claim 103, which does not. Therefore, Applicants have amended claims 64, 79, 104, and 123 to address this rejection. If this rejection was indeed directed to claim 103, Applicants request clarification of the rejection. Accordingly, this rejection should be withdrawn.

The Office Action (4/28/03, page 6, #23) has rejected claim 67 as being indefinite because the antecedent basis of "said nutritionally essential amino acids" in claim 58 was unclear. Claim 58 has been amended for clarification. Accordingly, this rejection should be withdrawn.

The Office Action (4/28/03, page 6, #24) has rejected claim 99 as being indefinite because the phrase "rather than" was unclear. Claim 99 has been amended for clarification. Accordingly, this rejection should be withdrawn.

Applicants note that claims 58, 69, and 97 recite that the amino acid changes alter the amino acid content of the protein by at least 5%. In view of the previous withdrawal of the rejection of claims under 35 U.S.C. §103, Applicants again emphasize that Dyer *et al.* actually teaches away from the use of methods that are not based on "[t]hree-dimensional structural information based on X-ray crystallographic analysis." Dyer *et al.* state (page 667, column I): "efforts toward protein engineering of seed storage proteins **have been frustrated primarily by lack of accurate structural information** of the target proteins **and by the inability to**

characterize structural alterations brought about by the introduced mutations" (emphasis added). Applicants also note that the Dyer *et al.* study was published in 1995, four years ***after*** the Goldberg reference cited in the Office Action. Thus, any attempt to combine these references is at odds with the insistence of Dyer *et al.* that X-ray crystallographic structural information was essential to progress and that protein engineering had been frustrated in the absence of such information. In conclusion, Dyer *et al.* **taught away** from the use of methods that did not depend on X-ray crystallographic structural information.

Applicants also again emphasize that in contrast to the teachings of Dyer *et al.*, the present invention provides the benefit that structural information is **not** required to make and use an altered protein. Therefore, because the combination of the Dyer and Goldberg references would not render the claims obvious, Applicants respectfully submit that the claims as amended should not be rejected under 35 U.S.C. §103.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§112, first and second paragraphs, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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